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10/575,736	10/11/2006	Michael V. Agrez	65350US(54086)	9415

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EXAMINER	
DUFFY, BRADLEY	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/575,736	AGREZ, MICHAEL V.	
	Examiner	Art Unit	
	BRADLEY DUFFY	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 January 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,86-90,92-99,101,104-106 and 108* is/are pending in the application.

4a) Of the above claim(s) *97* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,86-90,92-96, 98-99,101,104-106 and 108* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed January 7, 2011, is acknowledged and has been entered. Claims 1, 87, 88, 90, 94 and 101 have been amended. Claims 91, 100, 102-103 and 107 have been canceled. Claim 108 has been added.

2. Claims 1, 86-90, 92-99, 101, 104-106 and 108 are pending.

3. Claim 97 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species of invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement.

4. Claims 1, 86-90, 92-99, 101, 104-106 and 108 are under examination. The elected invention is drawn to a method for treatment of a cancer in a mammal, wherein cancer cells of the cancer express a MAP kinase and the method comprises treating the mammal with an effective amount of a polypeptide that consists of SEQ ID NO:7 and the elected species of signal peptide is a signal peptide comprising the amino acid sequence of SEQ ID NO:1, the elected species of β integrin subunit is β6 and the elected species of cancer is colon cancer. Additionally, the invention drawn to a method for treatment of a cancer in a mammal, wherein cancer cells of the cancer express a MAP kinase and the method comprises treating the mammal with an effective amount of a polypeptide that consists of SEQ ID NO:4 has been rejoined.

Election/Restrictions

5. In the response filed January 7, 2011, Applicant has continued to request rejoinder and notes that PCT Rule 13.4 states:

> "Subject to Rule 13.1, it shall be permitted to include in the same international application a reasonable number of dependent claims, claiming specific forms of the invention claimed in an independent claim, even where the features of any dependent claim could be considered as

constituting in themselves an invention."

In response, it is noted that PCT Rule 13.4 is subject to Rule 13.1 which states:

"The international application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept ("requirement of unity of invention")."

In this case, the pending claims are not distinguished over the prior art as detailed below, so the inventions are not linked to form a single general inventive concept.

Applicant is reminded upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141. However, as detailed below, there is presently no allowable generic claim.

Grounds of Objection and Rejection Withdrawn

6. Unless specifically reiterated below, Applicant's amendment and/or arguments filed January 7, 2011, have obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed July 7, 2010.

Claim Objections

7. Upon review and reconsideration, the objection to the claims is withdrawn, as the inventions may be subject to later rejoinder if a generic claim is found allowable.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. The rejection of claims 1, 86-90, 93-96, 98-99, 101, 104-106 and 108 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement,

is maintained. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Starting at page 3 of the response filed January 7, 2011, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but are not found persuasive for the following reasons:

In the response filed January 7, 2011, at page 4 Applicant appears to be arguing that "polypeptides that bind to a binding domain of MAP kinase," are adequately described in view of the disclosure at page 18, line 13 to page 19, line 3 that identifies a consensus sequence based on aligning binding domains for Erk2 of a β2, β3, β5 and β6 integrin and that since the claims recite modified sequences with 80% identity to a binding domain, the genus of polypeptides is “limited to a discrete, relatively small number of defined species”.

In response, it is first noted that the claims do not recite the sequences of β2, β3, β5 and β6 binding domains for Erk2 as set forth at page 18 or to modified sequences that conform with the consensus sequence set forth at page 18, line 13 to page 19, line 3 with 80% sequence identity or greater the sequences of β2, β3, β5 and β6 binding domains for Erk2 as set forth at page 18 and although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Accordingly, Applicants arguments are not found persuasive as claims 1, 86-90, 92-96, 98-99, 101 and 104-108 remain broadly drawn to methods for the treatment of a diverse genus of cancers in a mammal by treating the mammal with an effective amount of a structurally and functionally diverse genus of polypeptides that provide a cytoplasmic binding domain of a β integrin subunit for Erk2 or a modified polypeptide that has 80% sequence identify with the binding domain.

In the case, the recited genus of “polypeptides that provide a cytoplasmic binding

domain of a β integrin subunit for Erk2" need not have any particularly described structure and therefore, there can be no correlation of any particular identifying structural feature with any function of the recited polypeptides. Similarly, since the polypeptides that provide a cytoplasmic binding domain of a β integrin subunit for Erk2 need not have any particularly described structure one of skill in the art would not be able to immediately envision, recognize or predict the modified polypeptides that have 80% sequence identify with the binding domain which have the function of effectively treating cancer because the genus of polypeptides that provide a cytoplasmic binding domain of a β integrin subunit for Erk2 encompass polypeptides of undefined sequence and one of skill in the art could not identify modified polypeptides that have 80% sequence identify with polypeptides of undefined sequence.

Notably, with particular regard to the use of use functional language to define the boundaries of a claimed genus the Federal Circuit has recently clarified:

> For example, a generic claim may define the boundaries of a vast genus of chemical compounds, and yet the question may still remain whether the specification, including original claim language, demonstrates that the applicant has invented species sufficient to support a claim to a genus. The problem is especially acute with genus claims that use functional language to define the boundaries of a claimed genus. In such a case, the functional claim may simply claim a desired result, and may do so without describing species that achieve that result. But the specification must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus. Ariad Pharmaceuticals, Inc. v. Eli Lilly and Co. (Fed. Cir. 2010 <http://www.cafc.uscourts.gov/opinions/08-1248.pdf>) (En Banc Decision).

By way of further explanation, while the specification does provide guidance as to amino acid residues shared by binding domains that bind Erk2 based on an amino acid alignment, the specification lacks any other guidance as to what structural features of a binding domain are required for inhibition of growth of cancers expressing Erk2 or any guidance that any other species of peptides that fall within the consensus sequence can bind to Erk2 and inhibit growth of cancers expressing Erk2.

As set forth in the previous action, it is noted that it is well-established in the art that there is a high degree of unpredictability in modeling and predicting agents which will bind to any particular protein and inhibit that protein even when there is homology

between the peptides. For example, according to Tame (of record), for example, computational approaches to design or select drug reagents which bind protein targets are hindered by the complexity of the physical chemistry that underlies weak, non-covalent interactions between protein targets (e.g., a cell surface receptor) and small molecule ligands (e.g., peptides); see entire document (e.g., the abstract). In addition, Dixon (of record) points out that the evaluation (scoring) of potential solutions is still an area that needs improvement, especially when predicting protein-protein interaction because of limitations associated with reproducing the geometry of the complex; see entire document (e.g., the abstract). While there are many additional reasons that predictions based upon the results of such modeling approaches are inaccurate, it is noted that Lensink et al. (of record) very recently reviewed the performance accuracy of various different methods for predicting protein-protein interaction, reporting that significant numbers of "incorrect" determinations were made in blind analyses (i.e., without knowledge of the “correct” answer); see entire document (e.g., page 706, Table I). Lensink et al. concludes accordingly that their results "do not reveal a striking breakthrough in docking performance" in the past several years, despite some encouraging progress (page 717, column 1); and given such predictive inaccuracies, Lensink et al. adds that “current scoring methods are probably not sensitive enough” (abstract). Accordingly, one of skill in the art would not recognize that Applicant was in possession of the claimed methods of treating cancer that recite administering a genus of polypeptides that provide a cytoplasmic binding domain of a β integrin subunit for Erk2 or a modified polypeptide that has 80% sequence identify with the binding domain.

Accordingly, while the record as a whole and Applicant’s arguments have been carefully and fully considered, they were not found persuasive as the disclosure of a consensus sequence produced by aligning binding domains would not be considered to be representative of binding domains which would bind to Erk2 and also treat cancer. As evidenced by, Skolnick et al. (*of record*) in the previous action, the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (see, e.g., the abstract; and page 34, *Sequence-based approaches to*

function prediction). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see, in particular, the abstract and Box 2). Accordingly, as the consensus sequence was produced by aligning domains without any testing of additional representative species that fall within the consensus sequence genus one of skill in the art would not be able to immediately envision, recognize or predict which polypeptides that fall within the consensus sequence genus would bind to Erk2 and also treat cancer and those that would not.

Accordingly, after careful and complete consideration of Applicant's arguments and the record as a whole, for these reasons and as explained more fully in the Office action mailed July 7, 2010, the specification as filed would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed and this rejection is maintained.

10. The rejection of Claims 1, 86-90, 92-96, 98-99, 101, 104-106 and 108 under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for** methods of treating human cancers that express ERK2 in a mammal, comprising administering to said mammal an effective amount of a polypeptide consisting of the amino acid sequence of RSKAKWQTGTNPLYR (SEQ ID No: 4) or RSKAKNPLYR (SEQ ID No: 7), and **while being enabling for** methods of treating human cancers that express ERK2 in a mammal, comprising administering to said mammal an effective amount of a polypeptide consisting of the amino acid sequence of RSKAKWQTGTNPLYR (SEQ ID No: 4) or RSKAKNPLYR (SEQ ID No: 7), wherein the polypeptide is further coupled to a facilitator moiety, **does not *reasonably* provide enablement for** the full scope of the claimed methods, is maintained. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

In the response filed January 7, 2011, Applicant does not specifically address the

enablement rejection set forth in the previous action and the rejection is being maintained with respect to the amended claims as detailed below.

In this case, it is first noted that even while the elected invention is drawn to administering to a mammal an effective amount of a polypeptide consisting of the amino acid sequence of RSKAKWQTGTNPLYR or RSKAKNPLYR, and the specification teaches that these polypeptides are effective to inhibit the growth of human cancer cells expressing ERK2, the claims as amended are broadly drawn to treating any cancer from any species, i.e., the cancer need not express Erk2 (see e.g., claim 1). In this case, as evidenced by Tame, Dixon and Lensink et al (supra), it is highly unpredictable whether these polypeptides would inhibit growth of cancers that do not express Erk2 because the peptides bind to and inhibit Erk2 and it is highly unpredictable whether these polypeptides would bind to and inhibit other proteins expressed in the cancer, so it is highly unpredictable whether these polypeptides could be used to treat the full scope of cancers encompassed by the claims. Accordingly, one of skill in the art would be subject to undue and unreasonable expectation to determine how to treat the full scope of cancers, i.e., cancers which do not express Erk2, as encompassed by the claims with these polypeptides.

Secondly the specification does not contain any specific, non-general guidance that would allow one if skill in the art to make the genera of "polypeptides that provide a cytoplasmic binding domain of a β integrin subunit for Erk2" or "modified polypeptides that have 80% sequence identify with polypeptides of undefined sequence" which treat cancer in a mammal which would be representative of the full scope of these genera, so one of skill in the art would not be enabled to make the full scope of such polypeptides without undue experimentation as evidenced by the teachings of Tame, Dixon, Lensink et al, and Skolnick et al (supra); and if the full scope of polypeptides cannot be made without undue and unreasonable experimentation, the specification would not reasonably enable the skilled artisan to use the claimed polypeptides in the claimed methods without undue experimentation. In this case, while the specification provides a consensus sequence of binding domains that bind Erk2 produced by amino acid alignment of known binding domains, the specification lacks any specific, non-general

guidance as to the structure required for treating cancer and does not provide any evidence that the full scope of polypeptides encompassed by the aligned consensus sequence can bind to Erk2 and treat cancer. Accordingly, in view of the lack of predictability in the art, the minimal guidance disclosed in the specification with respect to polypeptides that can bind to Erk2 and treat all cancers and the broad breadth of the claims with respect to the claimed polypeptides and cancers treated, it is submitted that the quantity of experimentation which would be required in order to practice the full scope of the invention as claimed would be undue and/or unreasonable.

In conclusion, upon careful and full consideration of the factors used to determine whether undue experimentation is required and the record as a whole, for these reasons, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enabled the skilled artisan to make and use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation, and this rejection is being maintained.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. The rejection of claims 1, 86-90, 92-93, 98-99, 101, 104-106 and 108 under 35 U.S.C. 102(b) as being anticipated by Agrez et al (WO 2001/000677 A1, 2001, IDS filed 4/13/06), is maintained.

As drawn to the elected invention, the amended claims are herein drawn to methods comprising treating a mammal with colon cancer with an effective amount of a

polypeptide consisting of the amino acid sequence of RSKAKWQTGTNPLYR (SEQ ID No: 4) or RSKAKNPLYR (SEQ ID No: 7), wherein β6 integrin is not expressed by the cancer cells. The claims are further herein drawn to the polypeptide coupled to a peptide moiety that facilitates the polypeptide's passage into the cancer cells. Finally, the claims are herein drawn to the polypeptide being administered subcutaneously.

Starting at page 4 of the amendment filed January 7, 2011, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but are not found persuasive for the following reasons:

In the response filed January 7, 2011, Applicant appears to argue that Agrez et al does not teach methods of treating colon (bowel) cancers that do not express β6 integrin as Agrez et al teach that β6 integrin is expressed in at least 50% of colon (bowel) cancers at page 37 and that Agrez et al does not teach a linker region that links the opposite end regions of the binding domain together as presently claimed.

In response, Applicant's arguments are not found persuasive as a disclosure in Agrez et al requiring expression of β6 integrin in colon cancer for treatment of colon cancer could not be found. Notably, Agrez et al teach polypeptide inhibitors of ERK2 consisting of the amino acid sequence of RSKAKWQTGTNPLYR or RSKAKNPLYR, wherein the polypeptide is further coupled to a penetratin peptide that facilitates polypeptide's passage the into the cancer cells (see entire document, e.g., pages 13, 23, 24, 54, 55 and 60) and because these polypeptides inhibit Erk2 they would be expected to treat any cancer expressing Erk2 regardless of β6 integrin expression as other integrins and other pathways activate Erk2 to activate cancer cell growth. In further response and as further support for this position, Agrez et al teach that colon cancer cells designated SW480 do not express β6 integrin unless transfected with a β6 integrin expression vector and that the RSKAKWQTGTNPLYR polypeptide further coupled to a penetratin peptide that facilitates polypeptide's passage the into the cancer cells inhibits the growth of SW480 colon cancer cells which do ***not*** express β6 integrin (see Figure 31a and page 33).

Secondly, with respect to Applicant's argument that Agrez et al does not teach a linker region that linked the opposite end regions of the binding domain together as presently claimed, Agrez et al teach polypeptide inhibitors of ERK2 consisting of the amino acid sequence of RSKAKWQTGTNPLYR which is the elected invention as set forth in claim 92 and claim 92 depends from claim 1, so the teachings of Agrez et al anticipate claim 1. Then with respect to claims 88-90 Agrez et al teach the polypeptide RSKAKNPLYR which lacks the underlined linker sequence present in RSKAKWQTGTNPLYR and that the polypeptide of RSKAKNPLYR binds to Erk2 (see Figure 23), so the teachings of Agrez et al with respect to administering this peptide to colon cancer patients anticipate claims 88-90.

Accordingly, after careful and complete consideration of Applicant's response and the record as a whole, the rejection is being maintained for these reasons and the reasons of record as set forth in the previous action.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

15. The rejection of claims 1 and 94-96 under 35 U.S.C. 103(a) as obvious over Agrez (WO 2001/000677 A1, 2001, IDS filed 4/13/06) in view of Nadler et al (US 5,877,282, 1999, of record), is maintained.

Claims 94-96 are dependent claims further drawn to the polypeptide coupled to a facilitator moiety that is a growth factor signal peptide moiety that comprises the amino acid sequence of AAVALLPAVLLALLA, which facilitates entry of the polypeptide into the cells.

Starting at page 5 of the amendment filed January 7, 2011, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but are not found persuasive for the following reasons:

In the response filed January 7, 2011, Applicant reiterates the argument that Agrez does not anticipate any claims and that Nadler et al does not overcome any of the deficiencies of Agrez set forth in Applicant's response.

In response, Applicant's arguments with respect to Agrez were not found persuasive for the reasons set forth in the above 102(b) rejection and these reasons have been incorporated herein.

As set forth in the previous action, while Agrez teaches coupling the polypeptide to a penetratin peptide to facilitate entry of the polypeptide into cells, Agrez does not expressly teach the growth factor signal peptide with the amino acid sequence of AAVALLPAVLLALLA as a peptide that can facilitate entry of the polypeptide into cells.

This deficiency is made up for in the teachings of Nadler et al. Nadler et al teach that it is known in the art that the growth factor signal peptide with the amino acid sequence of AAVALLPAVLLALLA can be coupled to other polypeptides to facilitate entry of the polypeptide into cells (see entire document, e.g., column 8 and claim 7).

Thus, in view of these references, the claimed invention, as a whole, would have been obvious to one of ordinary skill in the art at the time the claimed invention was made because coupling the growth factor signal peptide with the amino acid sequence of AAVALLPAVLLALLA to other polypeptides to facilitate entry of the polypeptide into

cells was known and predictable in the art. Accordingly, one of ordinary skill in the art would not have found it inventive to predictably substitute the penetratin peptide for the growth factor signal peptide with the amino acid sequence of AAVALLPAVLLALLA, because they would have immediately envisioned that either peptide would be predictably effective in facilitating entry of the polypeptide into cells.

Accordingly, after careful and complete consideration of Applicant's response, the rejection is being maintained for the reasons of record as set forth in the previous action.

Double Patenting

16. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with

37 CFR 3.73(b).

17. The provisional rejection of Claims 1, 86-90, 92-96, 98-99, 101, 104-106 and 108 on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 217, 218, 219, 225, 238, 277 of copending Application No. 10/019,816 in view of Nadler et al (US 5,877,282, 1999, of record), is maintained. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

At page 5 of the amendment filed January 7, 2011, Applicant has indicated that the rejection will be addressed upon a finding that the pending claims are in condition for allowance, except for the double patenting rejection.

In response, the claimed inventions remain so substantially similar that any minor differences in the subject matter claimed in the instant application would be seen as an obvious variation of the subject matter claimed in the copending application and this rejection will be maintained until it is appropriately resolved.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

18. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

19. Claims 1, 86-90, 92-96, 98-99, 101, 104-106 and 108 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite,

since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 1 recites the broad recitation that the polypeptide has, i.e., comprises, a length of 25 amino acids followed by the narrow limitation or less. Accordingly, it is unclear whether the polypeptide has a maximum length of 25 or if the maximum length can be greater than 25 amino acids.

Accordingly, these claims fail to delineate the metes and bounds of the subject matter that Applicant regards as the invention with the requisite particularity and clarity to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph.

(b) The claims are also indefinite for reciting “or greater” in claim 1, line 9. This renders the claims indefinite because it is unclear what is considered to be greater since the "or greater” occurs at the end of a wherein clause. For example, is the binding of the binding domain greater, is the sequence identity greater than 80% or is something else greater? Without knowing what must be greater the claims cannot be unambiguously construed.

Accordingly, these claims fail to delineate the metes and bounds of the subject matter that Applicant regards as the invention with the requisite particularity and clarity to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph.

(c) The claims are also indefinite for reciting “providing” after “a polypeptide” in claim 1, line 3 as it is not clear what the metes and bounds are of a polypeptide *providing* a cytoplasmic binding domain. For example, is this a transitional phrase that indicates the polypeptide contains the cytoplasmic binding domain, can the polypeptide

provide the cytoplasmic binding domain by being conjugated to the cytoplasmic binding domain, or does the polypeptide provide the cytoplasmic binding domain in some other way? Without knowing the answer to this question the claims cannot be unambiguously construed. If “providing” it is intended to be used as a transitional phrase limiting the scope of the preceding “polypeptide”, then amending it to recite "comprising”, “consisting essentially of”, or “consisting of” would obviate this rejection.

If it is not a transitional phrase, then further amendment is requested to clearly identify how the polypeptide *provides* a cytoplasmic binding domain so that the metes and bounds of the claim can be unambiguously construed.

(d) The claims are also indefinite for reciting “incorporating” after “β integrin subunit” in claim 1, line 5 as it is not clear what the metes and bounds are of a β integrin subunit *incorporating* an amino acid linker region. For example, is this a transitional phrase that indicates the β integrin subunit contains the amino acid linker region, can the β integrin subunit incorporate the amino acid linker region by being bound to the amino acid linker region, or does the β integrin subunit incorporate the amino acid linker region in some other way? Without knowing the answer to this question the claims cannot be unambiguously construed. If “*incorporating*” is intended to be used as a transitional phrase limiting the scope of the preceding “β integrin subunit”, then amending it to recite "comprising”, “consisting essentially of”, or “consisting of” would obviate this rejection.

If it is not a transitional phrase, then further amendment is requested to clearly identify how the β integrin subunit *incorporates* an amino acid linker region so that the metes and bounds of the claim can be unambiguously construed.

Therefore, these claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

20. Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not

described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a NEW MATTER rejection.

In this case, claim 1 was amended in the response filed January 7, 2011, to recite “25 amino acids or less”.

At page 1 of the response filed January 7, 2011, Applicant has indicated that support for these amendments occurs throughout the specification as filed and in claims 87, 90 and 103.

Contrary to Applicant's assertion, however, it does not appear that the specification, including the claims, as originally filed, provides written support for the language of the claims.

In this case, page 15 sets forth the following relevant disclosure:

> Typically, a polypeptide of the invention or administered to a mammal in accordance with the invention will have a length of about 150 amino acids or less, more preferably about 75 amino or 50 amino acids or less and most preferably, about 40 amino acids or less. When the polypeptide is a fusion protein or agent incorporating a carrier moiety, the binding moiety that binds to the integrin will generally have a length of between about 5 to about 50 amino acids and more preferably, a length of between about 5 to about 35 amino acids.

Notably, this disclosure does not refer to polypeptides of 25 amino acids or less as instantly recited and the original claims did not recite polypeptides of 25 amino acids or less. Accordingly, it does not appear that the specification originally contemplated a genus of polypeptides of 25 amino acids or less. Therefore, given the apparent difference in the claims and that of the pertinent disclosures it is submitted that this clearly illustrates that such amendments have in fact introduced new concepts, thereby violating the written description requirement set forth under 35 U.S.C. §112, first paragraph.

Otherwise these issues might be resolved if Applicant were to point to other disclosures in the specification, including the claims, as originally filed, which are believed to provide the necessary written support for the language of the instant claims.

Conclusion

21. No claims are allowed.

22. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brad Duffy whose telephone number is (571) 272-9935. The examiner can normally be reached on Monday through Thursday 6:15 AM to 4:45 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Misook Yu can be reached on (571) 272-0839. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully,
Brad Duffy
571-272-9935

Respectfully,
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/bd/
Examiner, Art Unit 1643
February 28, 2011

/Misook Yu/
Supervisory Patent Examiner, Art Unit 1643